AREA OF FOCUS #6

AIDS

The human immunodeficiency virus (HIV) infection leading to the acquired immunodeficiency syndrome (AIDS) is a relatively recent epidemic and an important public health problem both in the United States and globally.

The four distinct groups of individuals in whom the epidemic is rapidly spreading are male homosexuals, injecting drug users, infants of untreated or undetected HIV-positive women, and heterosexual persons, principally in minority communities where HIV infection is facilitated by high rates of other sexually transmitted diseases (STD).

Over 600,000 persons have been diagnosed with AIDS in the United States. A larger number are infected with HIV, many of whom are not yet diagnosed. In the United States, African Americans and Hispanic or Latino Americans are disproportionately infected with HIV.

Persons infected with HIV may develop a multi-system dysfunction, and those with AIDS typically have severe abnormalities in many organ systems.

Persons infected with HIV with or without AIDS may develop severe metabolic abnormalities, including severe wasting syndrome.

Individuals co-infected with hepatitis C may follow a more virulent course to severe morbidity and/or death.

Development of HIV-related nephropathy may occur early in the course of the disease, with/without AIDS, and may progress to end-stage renal disease. Between 1993 and 1997, AIDS nephropathy was the reported cause of ESRD in 1 percent of all incident ESRD patients, but was the fourth leading cause of ESRD in African Americans.

Research Goal 1

To strengthen urological investigations of factors that influence sexual transmission of human immunodeficiency virus (HIV)

Current Activities

The current research portfolio is focused on transmission of HIV in semen, sites of HIV replication in the male genitourinary (GU) tract, effect of protease inhibitors on HIV titer in the male GU tract compared with effect in serum, infectivity of HIV in semen compared with serum, relationships between semen white cells and HIV levels, effect of vasectomy on HIV titer, and relationships between STD and HIV in semen. The level of funding in FY 1999 was approximately \$750,000.



Potential New Initiative

A clinical study of the effect of protease inhibitors on viral replication in semen vs. serum and basic research studies focusing on localization of HIV replication in the male GU tract, with and without vasectomy, will enhance our understanding of the urologic factors that influence HIV transmission.

Expected Outcome

The data from these studies on the effectiveness of protease inhibitors in reducing HIV titers and HIV infectivity in semen, comparing serum response to semen response, will ultimately help in targeting the appropriate site for eradication of the replicating HIV.

Action Plan

The expected mechanisms for funding include investigator-initiated research project grants (R01s) and Cooperative Agreements (U01s).

Research Goal 2

To understand, prevent, and treat the metabolic abnormalities and body composition changes associated with HIV and its therapy in minority populations

Current Activities

The advent of effective anti-retroviral therapies has resulted in a dramatic reduction in the mortality and morbidity associated with HIV infection. The incidence of wasting syndrome, once a major health concern amongst HIVinfected individuals, has been reduced dramatically. However, among certain segments of the population, the lack of appropriate health care and the concomitant prevalence of high-risk behaviors, such as intravenous drug abuse, have conspired to sustain both opportunistic infections and wasting. NIDDK supports several studies on both the etiology and potential treatment for wasting syndrome associated with HIV, including a trial of combination anabolic therapy. This trial includes a high percentage of minorities as subjects and has recently expanded to a fourth site with anticipation of even greater participation by minority individuals.

As the effectiveness of anti-HIV therapies has improved, a new set of metabolic complications has emerged. These complications included peripheral weight loss with or without apparent increased abdominal fat, possible bone loss, atherogenic lipid profiles, and diabetes. While a number of basic and clinical investigations into the pathophysiology

of this constellation of abnormalities have been initiated with funding from NIDDK, the prevalence and association with particular therapeutic agents have not been established. NIDDK, in collaboration with NIAID, NHLBI, and the Office of AIDS Research, has funded a nationwide multicenter. cross-sectional study (FRAM) to determine the extent of this problem. As minority individuals from Hispanic and African-American backgrounds are already disproportionately affected by HIV and are also at greater risk for diabetes and cardiovascular disease, the consequences of these metabolic complications may be particularly devastating in these populations. This study, which includes 16 sites across the country, began recruitment in April 2000, and has a target of 41 percent Caucasian and 59 percent minority representation, primarily African-American. This study has an ambitious schedule with plans to report results within 2 years of commencement of recruitment. The results should provide a strong scientific basis for development of potential therapies in addition to design of appropriate experiments to elucidate the pathobiology of these abnormalities.

Potential New Initiative

As data emerges from the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study, investigations will be initiated to take advantage of these results, particularly in respect to the potential disproportionate burden of these problems in minority populations. In addition, NIDDK is participating in an RFA entitled "Protease Inhibitor-Related Atherosclerosis in HIV Infection," which will support collaborations between basic and clinical investigators. NIDDK plans to give special consideration to those applicants who are focusing on minority populations.

Expected Outcome

The FRAM study sponsored by NIDDK should provide insights into the cause and potential racial/ethnic disparity in the extent of metabolic abnormalities associated with HIV. These results will provide the foundation for targeted studies on etiology and treatment in minority populations. Planning grants to develop recruitment strategies and increase the pool of qualified investigators working with ethnic/racial groups will enhance the likelihood of effective treatment for metabolic abnormalities in HIV within the populations most at risk.

Action Plan

The expected mechanisms for funding include pilot and feasibility grants (R21s), investigator-initiated research project grants (R01s), and Cooperative Agreements (U01s).

Research Goal 3

To understand and decrease the disproportionate burden of HIV nephropathy in African Americans and Hispanic/Latino Americans

Current Activities

This area of investigation includes extramural basic science grants and intramural investigations in the pathogenesis and the pathophysiology of HIV nephropathy. Some of these studies are directed at elucidating the mechanisms of HIV nephropathy in different racial and ethnic populations. There are studies specifically examining the genetic and other determinants of differential susceptibility to the development of renal disease in HIV-infected people and animal models. NIDDK invests approximately \$3 million yearly in this area of research.

Potential New Initiative

Support studies of the pathogenesis of HIV nephropathy and examination of the effects of highly active retroviral therapies on the progression of HIV nephropathy.

Expected Outcome

Effective antiretroviral therapy will prevent progression of HIV nephropathy to ESRD.

Action Plan

Mechanism of funding will be by R01s for the study of pathogenesis in humans. A Cooperative Agreement (U01) is expected to fund the treatment consortium.